CLINICAL RESEARCH PROTOCOL

Concurrent teleRehabilitation and Radiation (CoRR) for Patients with Gliomas

Clinical Trial Protocol Number: CoRR2024

Protocol Version 1.2, July 30, 2025

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SIGNATURE PAGE FOR SPONSOR

Title: **Concurrent teleRehabilitation and Radiation (CoRR) for Patients with Gliomas**

Protocol Version 1.2, July 30, 2025

Approved by the following:

Dr. Meiqi Guo

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Name	Signature	Date

Dr. Alan Tam

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Protocol Version Record

Version	Amendment	Date
1.0	Draft version for REB review	Oct 18th, 2024
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1.2	Amendment	July 30th, 2025

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Background

Primary brain tumors (PBTs), including gliomas (the most common PBT in adults), are a major public health burden worldwide.[1,2] Global incidence rates are increasing and can reach up to 26 per 100,000 person-years.[3] In Canada, ~6,000 patients per year and ~16 patients per day are diagnosed with PBTs.[4] Although PBTs represent <2% of all malignancies, they are second only to stroke as a cause of mortality from neurologic diseases.[1,5] Their functional consequences far outweigh their prevalence and subsequent high disability rates can severely strain healthcare systems.[1,5]

With recent advancements in multimodal interventions (e.g., neurosurgery, radiotherapy, systemic therapy), patients with PBTs can survive longer.[2,5] However, early and delayed treatment complications may occur and range from mild transient side effects to disabling long-term sequelae, such as sensorimotor, cognitive, and psychosocial impairments as well as deconditioning, negatively impacting the quality of life of survivors.[5,6] Studies have shown that interprofessional rehabilitation can help address these issues and provide holistic and tailored care to both inpatients and outpatients.[6,7]

Rationale

Even though rehabilitation is of paramount importance in patients with PBTs when compared to other malignancies due to their high risk of disability, it remains unclear when exactly rehab can be effectively and safely started due to a dearth of high-quality evidence and best practices.[7,8] Nonetheless, rehabilitation should be initiated at some point to prevent complications, manage impairments, and maintain patients' functional independence regardless of life expectancy.[9] The current brain cancer rehabilitation practice across Canada involves in-person service delivery in inpatient and outpatient settings **after** medical/surgical treatment and radiotherapy, respectively, if applicable. However, it is uncertain whether this practice represents the most effective model of care.

One of the goals of inpatient rehabilitation is to improve patients' functional abilities, facilitating their attendance and tolerance to radiation treatments, while outpatient rehabilitation is geared towards addressing the residual deficits arising from the cancer itself, the brain injury, as well as treatment complications.[5,10,11] While cranial radiation is a proven curative and palliative intervention for PBTs, [12] it is not without toxicity, including cognitive and physical decline.[13] There are various mechanisms by which radiation can induce brain injury, including reduction of neural precursors in the hippocampus, alteration of the cellular microenvironment, inflammation via oxidative damage, ischemia and neuronal excitotoxicity.[14] Whether concurrent rehabilitation can be beneficial as both modes of treatment target the same organ requires further study. We know from stroke rehabilitation that rehabilitation provided hyperacutely within 24 hours of the injury to the brain is associated with poorer functional outcomes when

compared to usual care.[15] A similar investigation on the timing of optimal rehabilitation in people with brain cancer is warranted.

While in-person rehabilitation remains the standard of care, the COVID-19 pandemic has accelerated the adoption of telerehabilitation, enhancing accessibility, participation, and patient experience for individuals with acquired brain injuries (ABI), and fostering improved clinical outcomes (e.g., to fatigue, depression, anxiety, insomnia, cognition, strength, balance and gait).[16–18] To our knowledge, no studies on interprofessional, synchronous telerehabilitation have been conducted in adults with PBTs.

Overall Study Objectives

We will conduct a pilot randomized controlled trial with an embedded qualitative component with the following objectives:

1. To evaluate the feasibility, safety, and preliminary effectiveness of an interdisciplinary synchronous telerehabilitation program consisting of video-based individualized physiotherapy (PT), occupational therapy (OT), and/or speech language pathology (SLP) sessions, compared with current standard-of-care, on physical function, cognitive function, confidence to self-manage care, and quality of life for participants who are **concurrently** undergoing radiation therapy for glioma,
2. To evaluate the feasibility of administering outcome measures of quality of life, recovery of impairment, fatigue and survival for a future definitive study
3. To understand the experiences of participants with telerehabilitation including the perceived impact on quality of life, as well as barriers and facilitators to participation

Hypotheses

We hypothesize that:

1. The telerehabilitation protocol will demonstrate sufficient feasibility (defined as ≥80% of participants completing the 8-week protocol) to support a larger, multisite randomized controlled trial.

Study Design

The CoRR Study will use a two-arm pilot randomized controlled trial design to compare feasibility and preliminary effectiveness of active telerehabilitation (intervention) versus usual care (control), and involve quantitative and qualitative methods of data collection.

Intervention groups

1. **Active Rehab** - outpatient rehabilitation delivered via synchronous, video-based telerehabilitation for 8 weeks; PTs, OTs and/or SLPs (depending on clinical need), twice per week for 50-minute sessions (for each discipline of clinical need) during Radiation Therapy (up to 8 weeks). Neurosurgeon or oncologist may also refer outpatient rehab through the Toronto Rehab

ABI Day Hospital after Radiation Therapy if a participant meets the Toronto Rehab ABI Day Hospital acceptance criteria

2. **Usual Care** - generic aerobic and strengthening exercise instructions and an 8-week subscription to BrainHQ during Radiation Therapy; Neurosurgeon or oncologist may also refer outpatient rehab through the Toronto Rehab ABI Day Hospital after Radiation Therapy if a participant meets the Toronto Rehab ABI Day Hospital acceptance criteria

Randomization

Participants will be stratified for glioma grade (grade ≤3, grade=4) and then randomly assigned to the 2 intervention groups using a 1:1 allocation ratio block design. The schedule will be randomly generated using the PLAN procedure (SAS 9.4, SAS Insititute, USA).

Blinding

Evaluators and the study statistician will be blinded to the group allocation, however, due to the nature of the intervention, participants and members of the research team cannot be blinded to group allocation.

Research Ethics

Research Ethics approval will be obtained prior to starting the trial. The trial will be conducted in accordance with applicable regulations and guidelines on current Good Clinical Practice (GCP) guidelines.

Participant Selection and Screening

The study aims to recruit up to 54 individuals who will undergo radiation therapy for intracranial gliomas from Princess Margaret Hospital Pencer Centre and Toronto Western Hospital neurosurgery service.

A member of the potential participants' circle of care (e.g., physical therapist, physician, social worker) will identify all patients who meet study inclusion and exclusion criteria:

Inclusion Criteria

1. 18 year of age or older;
2. Planned to undergo an initial course of radiation for a diagnosis of intracranial glioma (any grade)
3. Recent brain surgery (within 12 weeks)
4. Eastern Cooperative Oncology Group (ECOG) performance status ≥ 1 at time of enrollment
5. Have a caregiver, friend, or family member available to provide physical support during the initial assessment session and Active Rehab sessions
6. Eligible to be prescribed Brain HQ and home exercise
7. Have an email address, or caregiver, friend or family member has an email address

8. Have cognitive-communicative ability to participate as per clinical judgement;
9. Able to provide informed consent, or if not, availability of legal decision maker.
10. Access to a space with necessary therapy requirements (e.g. must have sturdy chair with armrests; if room is carpeted, must be low-pile, etc.);
11. Able to understand English to the point that they are able to follow instructions, and express levels of exertion, pain, distress, etc. as determined by the study team

Exclusion Criteria

1. Undergoing a repeat course of in-field repeat irradiation for a recurrent brain tumour;
2. Spinal glioma;
3. Currently receiving in-patient or outpatient rehabilitation;
4. Living in long-term care;
5. Severe vision or hearing loss, impacting ability to participate actively in rehab;
6. Planned surgery that would preclude or affect participation in the protocol
7. Contraindications to radiation therapy (e.g. pregnancy, or trying to conceive)

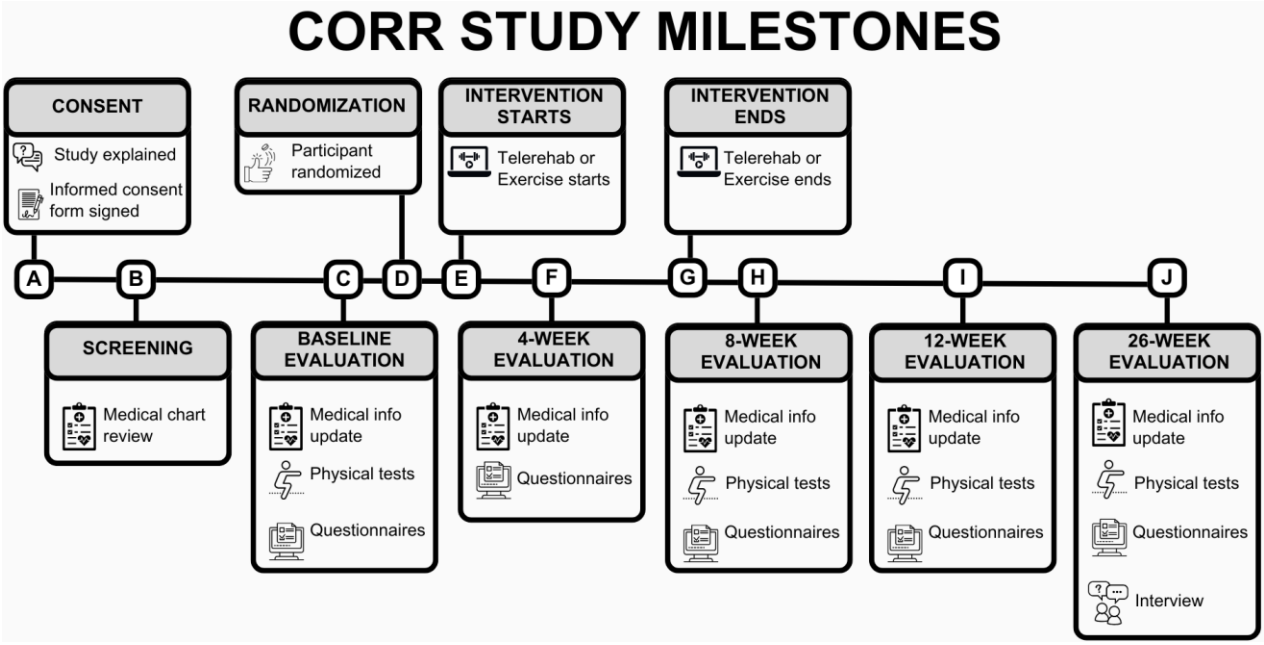
Inclusion and exclusion criteria will be assessed by reviewing the patient's medical and social history including review of the following screening data:

1. Glioma grade
2. Prior occurrence(s) of tumour
3. Presence of severe hearing/vision loss
4. Current participation in neuro-rehabilitation
5. Place of residence

The member of circle of care will inform potential participants about the study opportunity and share the recruitment materials containing the contact information of the research team. Once a patient has indicated their interest to a circle of care member, the circle of care member will pass on their contact information via phone or secure internal UHN email to the study coordinator, who will then approach the patient in person or via a phone call to explain the study, and ask if they would like to receive the consent form to review. If the patient prefers using e-mail for research-related communication, study coordinator will

obtain the patient's permission to use e-mail and will note it in the study files. The study coordinator will share a copy of the consent form via their preferred method (e.g. posted in the mail, e-mail or in person) with those who express interest and allow adequate time to read the consent form and discuss it with family and/or care providers. If the patient decides to proceed with the study, research coordinator will schedule a session to answer any questions and obtain consent. Participants will also be recruited through self-referral using study flyers posted in the designated areas at UHN.

CoRR Study Milestones and Procedures



Informed Consent

Informed consent will be obtained from potential participants (or their substitute decision maker where fully informed consent cannot be ascertained due to language or cognitive impairment) prior to beginning any study related activities.

Informed consent may be done in-person or virtually via RedCap e-consent, as per UHN's standard operating procedures for e-consent, depending on the participant's preference.

The informed consent process will involve an individual discussion with the participant about the nature of study procedures, interventions and assessments. A research team member will also explain reasonably anticipated benefits and potential hazards of the trial and any discomfort it may entail as well as alternatives to participating in the study.

The study team will be explaining and discussing the details in a language that is easy to comprehend. Participants will be encouraged to ask questions and take their time to consider and discuss the study with their families and healthcare providers. The study team will emphasize that participation is voluntary and refusal to participate in the study will not affect the quality of medical care. Participants will be informed that they are free to withdraw consent to participate at any time.

Participants will be informed that their medical and demographic data (glioma grade, time since diagnosis, tumour location, neurological deficits, prior occurrence(s) of tumour, other medical diagnoses, medications, current participation in neuro-rehabilitation and place of residence) that is necessary for conducting the study will be collected and that personal information will be treated as strictly confidential and will not be publicly available.

Participants will be informed in writing that their medical and social data relevant to this study will be stored and analyzed while maintaining confidentiality in accordance with local data protection laws. All data transferred to the eCRF (electronic Case Report Form) and any process derived from the eCRF will be de-identified.

A paper or an electronic informed consent form approved by the institutional Research Ethics Board (REB) will be reviewed, signed and dated by the participant and/or participant's substitute decision maker on one side and a delegated research team member on the other side. Participants will be provided with a copy of the signed informed consent form.

If new information becomes available that may be relevant to participants' willingness to stay in the study, the research team will inform the participants in a timely manner.

Should a protocol amendment be made, the informed consent form may be revised to reflect the changes in the protocol. In this case, the investigator will ensure that an amended informed consent form is reviewed and approved by the institutional REB, and that it is signed by all participants subsequently entered in the study and those currently in the study, if affected by the amendment.

An honorarium will also be provided as a token of appreciation for participants' time in the form of a $50 gift card to a grocery store/book store after the 8-week and another $50 gift card after the 26-week evaluations.

Baseline Evaluation

At baseline, prior to the intervention beginning, the following data will be collected over video conferencing or as a self-administered questionnaire:

1. Participant Demographic Information Form

2. Participant Personal Information Form
3. Berg Balance Scale
4. Timed Up and Go Test
5. 30 Sec Sit to Stand Test
6. The Arm Capacity and Movement Test (ArmCAM)
7. Brief Test of Adult Cognition by Telephone (BTACT)
8. Brief Visuospatial Memory Test – Revised (BVMT)
9. Sustained Attention to Response Task (SART)
10. Wechsler Test of Adult Reading (WTAR)
11. Perceived Medical Condition Self-Management Scale
12. EuroQol-5 Dimension 5 Level (EQ-5D-5L)
13. Fatigue Severity Scale

4-Week Evaluation

At the 4-week evaluation, we will collect the following data over video conferencing or as a self-administered questionnaire:

1. Berg Balance Scale
2. Timed Up and Go Test
3. 30 Sec Sit to Stand Test
4. The Arm Capacity and Movement Test (ArmCAM)
5. Brief Test of Adult Cognition by Telephone (BTACT)
6. Brief Visuospatial Memory Test – Revised (BVMT)
7. Sustained Attention to Response Task (SART)
8. Wechsler Test of Adult Reading (WTAR)
9. Perceived Medical Condition Self-Management Scale
10. EuroQol-5 Dimension 5 Level (EQ-5D-5L)
11. Fatigue Severity Scale
12. Medical Information Update Form

8-Week Evaluation

At the 8-week evaluation, we will collect the following data over video conferencing or as a self-administered questionnaire:

1. Berg Balance Scale
2. Timed Up and Go Test
3. 30 Sec Sit to Stand Test
4. The Arm Capacity and Movement Test (ArmCAM)
5. Brief Test of Adult Cognition by Telephone (BTACT)
6. Brief Visuospatial Memory Test – Revised (BVMT)
7. Sustained Attention to Response Task (SART)
8. Wechsler Test of Adult Reading (WTAR)
9. Perceived Medical Condition Self-Management Scale
10. EuroQol-5 Dimension 5 Level (EQ-5D-5L)
11. Fatigue Severity Scale
12. Medical Information Update Form

Any new medical diagnoses, adverse events, or changes in other medications will be noted.

12-Week Evaluation

At the 12-week evaluation, we will collect the following data over video conferencing or as a self-administered questionnaire:

1. Berg Balance Scale
2. Timed Up and Go Test
3. 30 Sec Sit to Stand Test
4. The Arm Capacity and Movement Test (ArmCAM)
5. Brief Test of Adult Cognition by Telephone (BTACT)
6. Brief Visuospatial Memory Test – Revised (BVMT)
7. Sustained Attention to Response Task (SART)
8. Wechsler Test of Adult Reading (WTAR)
9. Perceived Medical Condition Self-Management Scale
10. EuroQol-5 Dimension 5 Level (EQ-5D-5L)
11. Fatigue Severity Scale
12. Medical Information Update Form

Any new medical diagnoses, adverse events, or changes in other medications will be noted.

26-Week Evaluation

At the 26-week evaluation, we will collect the following data over video conferencing or as a self-administered questionnaire:

1. Berg Balance Scale
2. Timed Up and Go Test
3. 30 Sec Sit to Stand Test
4. The Arm Capacity and Movement Test (ArmCAM)
5. Brief Test of Adult Cognition by Telephone (BTACT)
6. Brief Visuospatial Memory Test – Revised (BVMT)
7. Sustained Attention to Response Task (SART)
8. Wechsler Test of Adult Reading (WTAR)
9. Perceived Medical Condition Self-Management Scale
10. EuroQol-5 Dimension 5 Level (EQ-5D-5L)
11. Fatigue Severity Scale
12. Medical Information Update Form
13. Semi-structured Interview about participant experiences with telerehab for those in the intervention group

Any new medical diagnoses, adverse events, or changes in medications will be noted.

The evaluators will be trained neuropsychologists/psychometrists, physiotherapists and occupational therapists. The participant's privacy during evaluations will be ensured by the use of pass codes to access the videoconference, personalized links or each participant to avoid unwanted participants, restricting screensharing to the evaluator, using the Lobby feature in Microsoft Teams, and the evaluators checking at the start of the evaluations if the participant is ok with their caregivers hearing the answers to questions asked.

Outcome Measurements

Primary Outcome

The primary outcome is feasibility of the intervention as measured by the percentage of participants who complete the intervention at week 8.

Secondary Outcomes

1. **Recruitment** - Screening and recruitment efficiency, number of participants recruited, percentage of patients approached who consent to the trial
2. **Adherence to interventions** - Percentage of rehab sessions attended, participant characteristics associated with adherence, percentage of participants who used BrainHQ/exercise programs and how much
3. **Retention** - Follow-up rates, time needed for data collection
4. **Participant Experience** - We will conduct semi-structured qualitative interviews with participants to better understand their telerehab experiences, the perceived impact of the intervention on quality of life, and barriers/facilitators for their participation in the intervention.

Safety - percentage of patients who experience adverse events, percentage of rehab sessions in which adverse events occurs, and adverse event type, severity and relatedness across both intervention groups.

Explanatory Variables to Characterize the Population:

Demographic and medical variables to characterize the participant population will be collected at baseline and will include age, sex/gender, place of residence, education, postal code, occupation, race and ethnicity, presence of caregiver at residence, duration of radiation therapy, and medical comorbidities and medications. To reduce the time demands placed on participants, a research assistant will collect the variables whenever possible from chart review, and ask participants to provide information on the variables not available from chart review.

Table 1. Measurement Tools and Testing Schedule

	Base-line (100 min)	4W (100 min)	8W (100 min)	12W (100 min)	26W (160 min)

Participant Demographic and Medical Information Form	X				
Participant Personal Information Form	X				
General Outcomes					
Feasibility and Safety Outcomes		X	X	X	X
Survival and Progression-Free Survival		X	X	X	X
EuroQol-5 Dimension 5 Level (EQ-5D-5L)	X	X	X	X	X
Fatigue Severity Scale	X	X	X	X	X
Physical outcomes measures					
Berg Balance Scale	X	X	X	X	X
Timed Up and Go Test	X	X	X	X	X
3m Walk Test	X	X	X	X	X
The Arm Capacity and Movement Test (ArmCAM)	X	X	X	X	X
Cognitive tests					
Brief Test of Adult Cognition by Telephone (BTACT)	X	X	X	X	X
Brief Visuospatial Memory Test – Revised (BVMT)	X	X	X	X	X
Sustained Attention to Response Task (SART)	X	X	X	X	X
Wechsler Test of Adult Reading (WTAR)	X	X	X	X	X
Qualitative component					
Semi-structured Interview (telerehab group only)					x

The majority of our outcome measures are self-report measures, which participants can either complete themselves and/or with assistance from a helper or research study staff based on participants' preferences. The outcome measures can be administered via a REDCap survey link sent to participants to enter their answers directly into REDCap or with assistance from a helper if they need it or via an online videoconference or telephone call between participants and study staff for direct entry of participants' answers into REDCap by research study staff (whichever method participants prefer).

Telerehab Intervention Protocol

Participants randomized into the active intervention group will be asked to participate in an outpatient neuro-rehabilitation program via telerehabilitation starting **concurrently** with their radiation therapy. Currently, patients with gliomas with rehabilitation needs start rehabilitation after their radiation therapy. The neuro-rehabilitation program used in the study will be 8-weeks in duration, and identical to what we currently offer in the ABI day hospital with the exception of 1) the rehabilitation program start concurrently with radiation and 2) the

therapies will delivered via telerehabilitation for all participants (compared to the ABI day hospital currently delivers up to 1/3 of their therapy sessions via telerehabilitation.
The key components of the outpatient neuro-rehabilitation program in this study are:

- Participants will discuss with the ABI day hospital service coordinator their impairments and goals, to understand if they need physiotherapy, occupational therapy and/or speech language therapy based on their clinical needs
- They will have twice a week, 50min sessions for each type of therapy
- Therapy will be delivered via Microsoft Teams and/or phone, based on therapists' clinical judgment

Adherence to telerehab protocol:

Adherence will be monitored using the Encounters data in EPIC, which displays "no-show" data to therapy sessions were attended. >80% attendance will be considered adherence to the telerehab protocol.

Risks related to telerehab:

Risk of falls, injury and cardiac events such as dysrhythmia, exertional angina, and muscular/joint strains. Telerehab groups will be supervised and emergency contact information will be provided by participants. Participants will obtain physician clearance for exercise and will have a caregiver present during telerehab sessions. All telerehab sessions provided as part of this study will be provided by specialized physiotherapists, occupational therapists and speech language pathologists with training in neuro-rehabilitation working in the Brain Rehab program, and they will be adhering to all Brain Rehab Program policies and procedures on safety during telerehab.

Principal Investigators will review and classify all adverse events as to severity, whether it was expected or not, and whether it was related to the intervention. Recruitment rate, dropouts at all stages, and reasons for non-completion will also be tracked.

Adverse events related to the telerehabilitation assignment or to other causes will be adjudicated by the PIs.

Study Sample Size and Statistical Analysis

Sample Size

A sample of 54 participants, 27 per arm, is planned for this study based upon an expected recruitment rate of a third (33%) of glioma patients seen in recruiting clinics (163 patient per annum). Feasibility trials are recommended to recruit between 20 to 50 participants per arm to adequately investigate if a protocol is feasible or not and a minimum of 22 participants per arm is required for precision

of the variance estimation. Loss to follow-up (LOF) will be analyzed as the primary outcome and the sample size will not be adjusted for LOF.

Statistical Analysis Plan

Primary Outcome

The primary outcome of the study is the feasibility of the protocol as defined as ≥80% of participants completing the 8-week protocol. It will be measured by percentage completed the 8-week protocol. If more than or equal to 80% of participants complete the 8-week protocol it will be deemed feasible. Rates of completion will also be compared by treatment arm at the Week 8 time point. Adherence to the study protocol will also be measured as attendance to telerehab sessions and ≥80% attendance will be defined as adherent. Percentage deemed adherent will be compared between the treatment arms at the 8-week time point.

Secondary Outcomes

Secondary outcomes (e.g. balance, mobility, quality of life, mood, etc.) are continuous in nature and will be analyzed using linear regression, adjusted for baseline. Time to all-cause mortality, time to disease specific mortality, and time to disease progression will be analyzed using Kaplan Meier estimators and log-rank tests.

Disease and demographic factors that may influence protocol attrition and adherence will be analyzed using a generalized linear mixed effects model with an assumed unstructured covariance matrix structure and robust sandwich estimation.

To assess the safety of the protocol, the number, type, and severity of SA events will be reported as a cumulative incidence and compared between treatment arms using a Poisson regression.

Since these analyses are hypothesis generating, complete-case analyses will be used, p-values will not be listed and 95% confidence intervals of estimates and change scores will be used instead so the study results can be interpreted in context. The standard deviation of changes in secondary outcome measures will be used for sample size calculations for future full-scale studies.

Missing Data

Missing data for secondary measures will be assessed for quantity and nature of missingness. As secondary analyses are hypothesis generating, whole case analysis will be used even if >5% are missing data. Although the baseline values are also required for the secondary outcome analysis, we anticipate missingness

will be extremely infrequent as REDCap will be used for data collection and missing completely at random (MCAR) so that no bias will be incurred by dropping those cases from the analysis. Participants that drop out prior to completion of protocol will be right censored for survival analyses.

Descriptive Variables

Baseline descriptive variables will be analyzed using standard methods as appropriate for the variable type (e.g. continuous, binary, ordinal, etc.) and empirical-derived distribution functions (e.g. parametric or non-parametric). To assess performance of proposed randomization stratification to inform future full-scale trials, baseline covariate balances between treatment arms will be compared using differences in empirical cumulative density functions (eCDF) and variance ratios.

Subgroup Analyses

Exploratory subgroup analyses will analyze group differences in demographic factors like age, disease factors such as tumor grade, tumour location and deficit type (e.g. physical, cognitive, communication, etc.) on secondary outcome measures using linear mixed effects modeling for measures repeatedly administered following randomization. As these are exploratory in nature and under-powered to sufficiently detect group differences, effect estimates and their 95% CI will be reported and p-values will not be reported.

Thematic analysis will be used to analyze the collected data. The first five interview transcripts will be initially coded by two members of the research team, and they will then meet to compare their codes. This step will allow for enhanced reflexivity and ensure rigour. A coding framework will be developed and applied to the remaining transcripts.

To facilitate the organization and analysis of the qualitative data, the transcripts, will be entered into NVivo 11. Following this, the codes will be clustered into groups or categories (i.e., codes that share similar meanings) and the predominant themes will be identified.

To maximize credibility and trustworthiness, additional members of the research team will meet with the two members of the research team over several meetings to discuss the developing analysis. New themes will also be discussed. Together, they will explore various thematic maps until consensus is reached and theme labels are agreed upon. The two members of the research team will analyze the remaining data. To protect anonymity, quotes exemplifying the various themes will not include any identifying details on the participants.

Trial Safety, Fidelity and Implementability Analyses

Recruitment rate, number and type of adverse events, number and reasons for dropouts, and numbers lost to follow-up will be summarized. At the end of the trial, semi-structured interviews will be completed with participants who have been randomized to receive telerehabilitation intervention to further explore the barriers and facilitators.

Participant Withdrawal

Reasons for withdrawal

Participants may withdraw or be withdrawn from the trial for any of the following reasons:

- Participant withdraws further participation in trial for any reason
- Participant becomes unable to complete trial intervention and/or complete assessment visits)
- Any medical condition that, in the opinion of the PI, may jeopardize the participant's safety if they continue in the trial

Documenting participant withdrawal

In all circumstances, reasons for withdrawal will be collected and all participants will be followed through to the trial's conclusion with previously stated outcome measures performed (timing is outlined in Table 1), as the main analysis will be an intention to treat analysis. This will, of course, be subject to the participant's continued consent to return for these assessments. Participants who withdraw consent will be advised to follow up with their regular health care provider.

Participants who are withdrawn or withdraw from active treatment will not be replaced.

Discontinuation Criteria

As stated above, an individual participant who suffers a Serious Adverse Event (SAE) judged to be related to the intervention will lead to discontinuation of the intervention. Principal investigators will be responsible for initiating appropriate medical care of participants at their site, and any rescue procedures will follow the best standard of care. Any events will be recorded. Unblinding of the participant allocation can be done if needed by the treating healthcare team.

For the trial as a whole, there are no planned interim analyses for efficacy or futility.

Adverse Events and Serious Adverse Events

Definition of an Adverse Event

An adverse event (AE) is an untoward medical occurrence in a participant that occurs during the course of the clinical trial which may or may not have a causal relationship with the trial procedures. An AE can be any unfavourable or

unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with a trial procedure.

Definition of a Serious Adverse Event

A SAE is defined as an AE that results in any of the following outcomes:

- Death
- Life-threatening situation (participant was in immediate risk of death at the time of the event. However, an event that might have hypothetically caused death if it was of greater severity is not included.)
- New in-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability or incapacity
- Important medical events not resulting in death, be life-threatening, or requiring hospitalization but may jeopardize the participant and may require medical or surgical intervention to prevent one of the above outcomes (based upon appropriate medical judgment)

Handling of Serious Adverse Events Principal investigators will be responsible for initiating appropriate medical care of participants during the study, in connection with trial procedures and assessments, and for monitoring the safety of participants.

All SAEs will be assessed during the course of the trial. At the beginning of every assessment session participants will be asked if they have experienced any AEs. Therapists routinely ask patients about adverse events that occur as the result of therapy, and they will be asked to relay this information to the Principal Investigators. In case an SAE is reported, the delegated study clinician who examines and evaluates the participant will determine the event's causality to the trial's procedures, based on temporal relationship and his/h
r clinical judgment. **It is the responsibility of the Principal Investigators to ensure all SAEs are assessed to determine causality, that is, to determine the likelihood that the SAE was caused by a study intervention.**

Determining causality of Serious Adverse Events

Degree of certainty about causality will be graded as follows:

- **Definitely Related:** Clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
- **Probably Related:** Evidence to suggest a causal relationship and the influence of other factors is unlikely.
- **Possibly Related:** Some evidence to suggest a causal relationship but the influence of other factors may have contributed to the event.
- **Unlikely:** The temporal relationship to the trial procedures makes a causal relationship improbable and/or the SAE is more likely due to other factors such as concomitant medication(s) or concomitant disease(s).

- **Not related:** The SAE is completely independent of trial procedures, and/or evidence exists that the event is definitely related to another etiology.

Documenting Serious Adverse Events
Pre-existing conditions will be recorded at the baseline visit following participant enrolment (including start date of the condition, frequency, and severity). After the participant signs the informed consent form any worsening of these conditions will be documented.

SAEs experienced by the participant between the signing of the Informed Consent and completion of the final follow-up appointment (the 26-week visit) will be recorded in the electronic case report form (eCRF).

Following up on Adverse Events
The principal investigators will follow participants with AEs until the events have subsided, the conditions are considered medically stable, the investigator considers it medically justifiable to terminate follow-up, or the participants are no longer available for follow up. Participants who discontinue due to adverse events will be treated and followed according to established medical practice. All pertinent information will be entered into the eCRF.

All SAEs should be monitored until resolved or until the SAE is clearly determined to be due to a participant's stable or chronic condition or intercurrent illness(es).

Reporting Serious Adverse Events
AEs experienced by the participant between the signing of the Informed Consent and completion of the final follow-up appointment (the 26-week visit) be reported to the principal investigator. The study team will report SAEs and Safety Reports to the UHN REB as per institutional requirements.

Data Collection and Methodology

All eligible participants will be consented prior to the initiation of any portion of the study assessments and intervention. The principal Investigator will review the baseline data and ensure that the participant meets the eligibility criteria and has provided informed consent.

Data will be managed in accordance with good clinical practices (GCP) for research trials involving human subjects.

The CRFs will be completed in a timely manner. All study records will be kept in accordance with applicable laws and regulations.

Record Retention
All trial records will be maintained and retained for a period of 10 years per current University Health Network Regulations.

Confidentiality and Participant Data Protection
The participants will be informed that data will be stored and analyzed by computer. The data will be stripped of participant identifiers prior to storage and a study ID will be assigned to each participant upon enrollment into the study. The document linking the study ID to the participant's name will be kept separately from the other files in a secure location. All participant information will be kept confidential and the participant will not be recognizable in data submitted for publication.

Records for each participant in the study will be de-identified and maintained in separate files in a secure, limited access location at the study site.

Publications
The results and experiences derived from this study will be jointly published by the investigators in the appropriate medical journals and presented at professional conferences.

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